DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of "m", MIP-1β, as the species of agonist and "r", leukemias, as the species of diseases/disorders/tissues in the reply filed on 08 August 2008 is acknowledged.

Claims 1-9 are under consideration in the instant application as they read upon the elected species of MIP-1β and leukemias.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

1. The disclosure is objected to because of the following informalities:

2. The specification contains a Figure at page 8. This Figure should be removed and included as Figure 2 in the drawings. MPEP §608.01 and 37 CFR 1.58 specifically state that "The specification, including the claims, may contain chemical and mathematical formulae, but shall not contain drawings or flow diagrams".

3. The specification is missing headings for the detailed description of the invention and the brief description of the figure. Applicant is also reminded about the suggested arrangement of the specification.

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate correction is required.

Claim Objections

4. Claims 1, 4, and 6 are objected to because of the following informalities:

5. Claims 1 and 4 use the acronyms "CCR3", "CCR6", "CCR8", "SDF-1" without first defining what it represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

6. In claim 6, line 2, the word "are" should be amended to recite the singular, "is".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph and 35 USC § 101

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 6-9 are indefinite because claims 6 and 7 recite the limitation "the host patient" in lines 2 and 1, respectively. There is insufficient antecedent basis for this limitation in the claims. It is noted that claim 6 depends upon claim 5. However, claim 5 does not recite “host patient”.

9. Claim 4 recites the limitation "hematopoietic stem cells" in 3. There is insufficient antecedent basis for this limitation in the claim. It is noted that claim 4 depends upon claim 1. However, claim 1 does not recite “hematopoietic stem cells”.

10. Claim 2 is indefinite because it recites “improving the homing of stem cells". It is not clear where the stem cells are going since stem cells can be found in many different places in the body. Bone marrow? Blood? Tissues? Organs? It is also not clear if the stem cells referred to in claim 2 are endogenous in a patient or are transplanted.

11. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and

Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "liver stem and progenitor cells", and the claim also recites "(oval cells)" which is the narrower statement of the range/limitation. Claim 3 also recites the broad recitation "skeletal muscle stem and progenitor cells", and the claim also recites "(satellite cells)" which is the narrower statement of the range/limitation.

12. Claims 1-9 provide for the use of an agonist, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

13. Claims 1-9 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of using macrophage inflammatory protein-1β (MIP-1β) for the treatment of progenitor and stem cells prior to and/or in the course of transplantation of the cells. Claim 2 recites that the use is for improving homing of the stem cells. Claim 4 recites that the use is to increase the sensitivity of hematopoietic stem cells to SDF-1 indcued cellular signals. Claim 5 recites that the use is for the treatment of leukemias. Claim 6 recites that the host patient is not conditioned. Claim 7 recites that the host patient is conditioned under sublethal, lethal, or supralethal conditions.

The specification of the instant application teaches a prophetic method of improving the successful homing of hematopoietic stem cells by contacting the hematopoietic stem cells in vivo or ex vivo with an agent that is at least one agonist of receptors CCR3, CCR6, or CCR8 (page 5, lines 23-27). The specification also discloses a prophetic method of improving the homing of hematopoietic stem cells in a host patient by applying into the patient which is receiving stem cell transplantation prior to and/or in the course of stem cell transplantation in vivo at least one agent which is an agonist of CCR3, CCR6, or CCR8 receptors (page 5, lines 28-33). The specification teaches that the agent is used for the treatment of leukemias (page 5, lines 14-22). However, the specification does not teach any methods or working examples that indicate MIP-

1β improves the homing of stem cells or progenitor cells, increases the sensitivity of stem cells to SDF-1 induced cellular signals, or treats leukemias. The specification also does not teach any methods or working examples wherein MIP-1β is utilized prior to or during the course of transplantation of progenitor or stem cells. The state of the art at the time the instant invention was made teaches that MIP-1β signals through the chemokine receptors, CCR5, CCR1, and CCR2b (Menten et al. Cytokine Growth Factor Rev 13: 455-481, 2002; page 466, column 1, first paragraph), which is contrary to the instant claims and specification which recite the use of an agonist of receptors selected from the group consisting of CCR3, CCR6, or CCR8. Menten et al. disclose that T lymphocytes migrate towards MIP-1β, as do natural killer cells, dendritic cells, and coronary endothelial cells (page 463, column 2; page 464, column 1; page 464, first full paragraph in column 2). Broxmeyer et al. teach that MIP-1β does not influence colony formation by myeloid progenitors (J Immunol 150(8): 3448-3458, 1993; page 3451, column 1 and the top of column 2). The prior art is silent as to the activity that MIP-1β has on the mobilization, migration, homing, and SDF-1 induced cellular signals of progenitor and stem cells. Thus, in view of the state of the art and lack of guidance from the instant specification, one skilled in the art would not be able to predict that MIP-1β *in vitro*, *ex vivo*, or *in vivo* (1) is useful for progenitor or stem cell transplantation, (2) can improve the homing of progenitor cells or stem cells, and (3) can increase cell sensitivity to SDF-1 induced cellular signals. Undue experimentation would be required of the skilled artisan to determine such.

Furthermore, the skilled artisan must also resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of MIP-1β to be utilized in the claimed method. Broxmeyer teaches that within the microenvironment in which they reside,

stem and progenitor cells are subjected to the influence of a number of different cytokines at any one time (In t J Hematol 74: 9-17, 2001; page 10, column 1, 1st full paragraph). Broxmeyer adds that a true understanding of potential physiological effects requires an evaluation and examination of how combinations of molecules elicit intracellular signals that influence the proliferation, survival, and homing/migration of hematopoietic stem and progenitor cells (page 10, column 1, 1st full paragraph). Thus, one skilled in the art would not be able to predict the activity of MIP-1β *in vivo* due to the presence of other growth factors, cytokines, chemokines, etc.

Finally, the specification of the instant application does not provide a nexus between MIP-1β and treatment of leukemias. In fact, Kothapalli et al. teach that large granular lymphocyte leukemia (often associated with autoimmune disorders) is characterized by increased production of chemokines such as MIP-1β (Int J Oncol 26: 529-535, 2005; page 529, 1st full paragraph in column 2; page 530, Figure 1B; page 531, Table I). Thus, one skilled in the art would not be able to predict that administration of MIP-1β would treat any leukemias. A large quantity of experimentation would be required of the skilled artisan to determine if MIP-1β is able to treat all possible leukemias. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Due to the large quantity of experimentation necessary to utilize MIP-1β to (1) improve the homing of progenitor cells or stem cells, (2) increase cell sensitivity to SDF-1 induced cellular signals, (3) aid in progenitor and stem cell transplantation, and (4) treat leukemias; the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same; the complex nature of the invention; the state of the prior art (see Menten et al., Broxmeyer et al., Broxmeyer, and Kothapalli et al); the unpredictability of the effects of MIP-1β *in vitro*, *ex vivo*, and *in vivo*; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Broxmeyer et al. (J Immunol 150(8): 3448-3458, 1993).

Broxmeyer et al. teach that myeloid progenitor cells are incubated with MIP-1β, thus meeting the limitations of claim 1 (see page 3451, column 1; page 3451, top of column 2; Figures 1 and 2).

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Minano et al. J Physiol 491(1): 209-217, 1996 (teach the administration of MIP-1β into the anterior hypothalamic, preoptic area (AHPOA) of rats)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
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